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A Remarkable Adenine-Binding Cleft Based On A Hydroxyimide Scaffold

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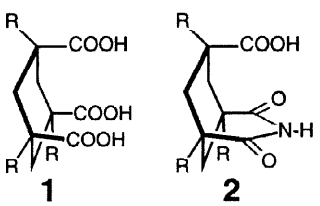
Abstract: The synthesis and binding properties of a molecular cleft for adenine recognition based on a new hydroxyimide scaffold is described. NMR titration experiments in various solvents as well as isothermal titration calorimetry results are presented which demonstrate that, in chloroform, the cleft gives association constants for 9-ethyladenine that are 20 times greater than for the corresponding cleft derived from Kemp's triacid.

Over the last few years, model studies in molecular recognition have contributed to the development of a wide range of novel molecular devices.[1] Perhaps one of the more versatile scaffolds for the assembly of abiotic receptor models has been Kemp's triacid **1**.[2] By virtue of its ability to preorganize functionality, triacid **1** is being used for a wide range of other applications, including catalysts[3], chiral auxiliaries[4] and proton sources,[5] transport mediators,[6] sensors,[7] replicators,[8] biophysical probes,[9] even combinatorial peptidomimetic libraries.[10]

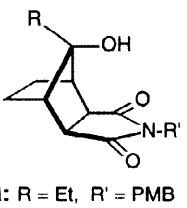
We have reported the synthesis of tricyclic hydroxyimides **3** and their application for the modular assembly of receptor models.[11,12] Scaffolds **3** are versatile isosteres of Kemp's imide acid **2** and are much easier to functionalize *via* a single divergent handle ("R"). The "R" group can, *inter alia*, modulate solubility or tether the device to a solid support (*via* **3c**).[13]



1

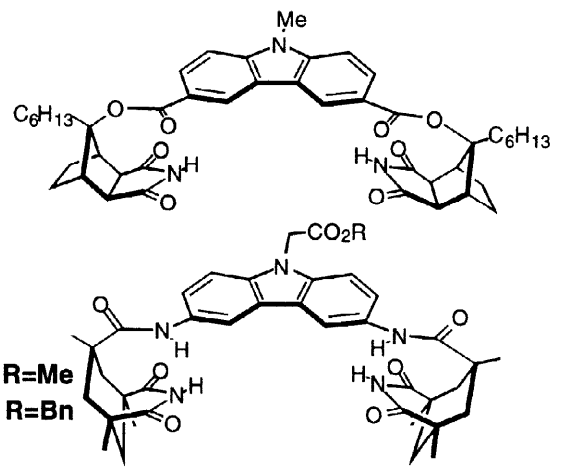
R = Me, Pr, CH_2OBn, CH_2OH

2



3a: R = Et, R' = PMB
3b: R = $C_4H_9C{\equiv}C$, R' = BOM
3c: R = $THPOC_4H_8C{\equiv}C$, R' = BOM

4



5a: R=Me
5b: R=Bn

Inspired by the versatile adenine-binding clefts **5** derived from Kemp's triacid[2a-d,14] and in order to assess

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the functionality of modular scaffold **3**, we wish to report the synthesis and binding properties of the cleft homolog **4**.

Cleft **4** was synthesized from hydroxyimide **3b** by a straightforward esterification and deprotection sequence. Accordingly, treatment of the potassium alkoxide of **3b** with 9-methyl-carbazole-3,6-dicarbonyl dichloride[15] in THF afforded the N-BOM-protected cleft (BOM = CH_2OBn) in 25% yield. Hydrogenolysis of the benzyl groups and ammonolysis of the resulting bis-N-hydroxymethylene imide[16] afforded cleft **4** in 65% yield.

Dilution studies of **4** by ^1H NMR revealed negligeable self-association in the 7 to 2 mM range in $CDCl_3$ with the imide singlet remaining between 7.6 and 7.4 ppm. By comparison, the imide NH in clefts **5** appears at ≈10.7 ppm, due to intra-molecular imide-imide H-bonded contacts.[2c] The conjugation of the ester carbonyls to the carbazole in **4** may disfavor the formation of such conformers.

An attempted NMR titration[17] of **4** with the benchmark 9-ethyladenine (9-EtA) in $CDCl_3$ showed very strong 1:1 association as the saturation of **4** was complete upon addition of a single equivalent of 9-EtA. As 9-EtA was added, the imide NH of **4** broadened and disappeared into the baseline, only to reappear at 12.9 ppm (at ≈ 0.5 equivalent of 9-EtA). This new imide signal remained at 12.9 ppm and sharpened until one full equivalent of guest had been added. Upfield complexation-induced shifts (CIS) of the carbazole and N-Me protons ranged from 0.03 to 0.38 ppm. Evidently, the strength of association and resulting slow-exchange behavior, precluded the measurement of K_a by NMR. In contrast, the comparable clefts **5a** and **5b** returned measurable K_a values of 21000 and 15000 M^{-1}, respectively.[2c]

To assess the binding of cleft **4** in a more competitive environment, titrations were carried out with 9-EtA in DMSO-d6/$CDCl_3$ mixtures.[18] The CIS recorded during the titrations in 20% and 40% DMSO/$CDCl_3$ were in complete agreement with the stacked chelation model (Figure 1). The upfield CIS due to stacking were greater in 40% DMSO/$CDCl_3$ compared to 20%, and suggest tighter stacking as the overall polarizability of the solvent decreases.[19]

Quantitative treatment of the saturation data with HOSTEST[20] gave excellent correlations to the simple 1:1 binding model, yielding K_a values of 8460 ± 350 and 467 ± 13 M^{-1} in 20% and 40% DMSO/$CDCl_3$, respectively.[21] These values are very high considering that the binding occurs primarily through H-bonding and π-stacking, and that DMSO is a strong competitor for the H-bond donor sites on both host and guest.

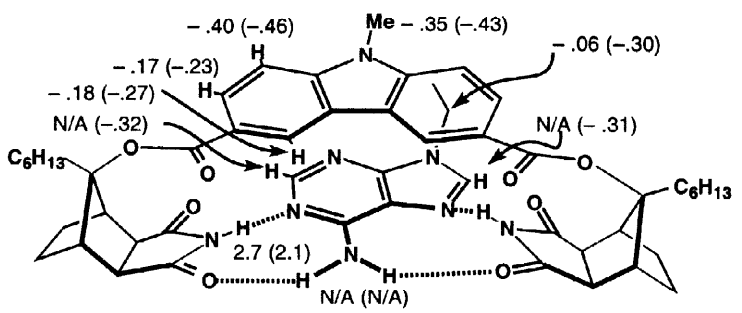

Figure 1. Complexation-induced shifts (CIS, δ ppm) for the titration of **4** with 9-ethyladenine (9-EtA) in 20% DMSO-d6/CDCl3 (and 40% DMSO-d6/CDCl3 in parentheses) at 8 equivalents added guest. CIS for 9-EtA protons were evaluated by comparing the solution with the highest **4**:9-EtA ratio (6:1) and pure guest at the same concentration. N/A: not availabe due to peaks hidden under more intense host signals.

These titration results warranted a quantitative reexamination of the binding experiments in $CDCl_3$ so the host-guest system was subjected to isothermal titration calorimetry[22] (Table I). The calorimetry experiments reveal an average association constant of 400000 M^{-1} for **4**/9-ethyladenine in $CDCl_3$ which is greater than the reported values for homologs **5a-b** by at least one order of magnitude. Quantitatively, the ΔH and ΔS values agree with a picture of optimal enthalpic contributions from the two imide-purine contacts within a well

preorganized environment, in $CDCl_3$.[2d,23]

Table I. Isothermal Titration Calorimetry (ITC) of Cleft **4** with 9-EtA in $CHCl_3$.

$[H]_o$[a]	K_a (M^{-1})	ΔG^{298} [b]	ΔH [b]	ΔS (e.u.)
0.80	436000 ± 60000[c]	-7.7	-10.7 ± 0.08[c]	-10.0
1.08	364000 ± 28000[c]	-7.6	-10.9 ± 0.05[c]	-11.2

[a] Initial concentration of **4** (mM). [b] kcal/mol. [c] From Origin™ 2.9 ITC data analysis.

Entropic solvophobic effects cannot account for the different binding properties of **4** and **5** since the comparative analysis was done in $CDCl_3$.[24] Likewise, van der Waals interactions cannot explain the results since the π-overlap in the two host-guest complexes should be very similar.

At first glance, receptors **4** and **5** appear to be isosteric except for the inversion of the acyl linkages. However, the vastly different chemical shifts for the imide of **4** and **5** in $CDCl_3$ suggests otherwise; this can be rationalized by invoking ester/carbazole coplanarity in **4** and intramolecular imide-imide contacts in **5**. On that basis, there would be an added enthalpic cost for chelating 9-EtA within clefts **5a-b**. It is also interesting to note that cleft **4** cannot take advantage of bifurcated H-bonding to reinforce the binding of 9-EtA (between the ester carbonyl and the 6-NH_2 group of 9-EtA which is already H-bonded to the imide carbonyl) yet returns much higher K_a values than the amide counterpart **5**.[2e,25]

The binding results are in agreemeent with the electrostatic model for π-stacking formalized by Sanders and Hunter.[26] The model is based on the attractive interactions between π-electrons of one ring and the σ-framework of the adjacent ring, which can outweigh unfavorable contributions such as π-π repulsion of the two rings. Accordingly, 9-EtA will prefer to stack to a more π-deficient aryl ring, in a face-to-face geometry. Due to the π-polarization of the conjugated carbonyl in **4**, the carbazole surface will be electron poor relative to **5**[27] and, as a result of the reduced π-π repulsion, should give more favorable π-stacking between host and guest. The ester carbonyl in **4** can decrease the London dispersive contribution of the carbazole towards π-stacking compared to **5**. However, this contribution should be less important in the highly polarizable $CDCl_3$.

This study has demonstrated that hydroxyimides **3** are valuable scaffolds for the modular assembly of molecular devices. Seemingly subtle adjustments of a molecular assembly can enhance a molecular recognition event by more than one order of magnitude in K_a. We are investigating the application of scaffolds **3** for the design of novel peptidomimetic libraries and chiral catalysts by combinatorial synthesis, and will report on our findings in due course.

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REFERENCES AND NOTES

1. (a) "Molecular Recognition", Gellman, S.H. Ed., *Chem. Rev.* **1997**, *97*, 1231-1734. (b) Hamilton, A.D. Ed. *Tetrahedron* (Symposia-in-print number 56) **1995**, *51*, 343-648.
2. For example, see (a) Kato, Y.; Conn, M.M.; Rebek, J.Jr. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 1208-1212. (b) Kato, Y.; Conn, M.M.; Rebek, Jr., J. *J. Am. Chem. Soc.*, **1994**, *116*, 3279-3284 (c) Conn, M.M.; Deslongchamps, G.; de Mendoza, J.; Rebek Jr., J., *J. Am. Chem. Soc.*, **1993**, *115*, 3548-3557. (d) Tjivikua, T.; Deslongchamps, G.; Rebek, J. Jr. *J. Am. Chem. Soc.*, **1990**, *112*, 8408-8414. (e) Huc,

I.; Rebek, J. Jr. *Tetrahedron Lett.* **1994**, *35*, 1035-1038. (f) Jeong, K.-S.; Cho, Y.L. *Tetrahedron Lett.* **1997**, *38*, 8337-8340.
3. Tsao, B.L.; Pieters, R.J.; **Rebek, J. Jr.** *J. Am. Chem. Soc.*, **1995**, *117*, 2210-2213.
4. (a) Curran, D.P.; Jeong, K.-S.; Heffner, T.A.; Rebek, J. Jr. *J. Am. Chem. Soc.*, **1989**, *111*, 9238-9240. (b) Jeong, K.-S.; Parris, K.; Rebek, J.Jr. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 555-556.
5. a) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *SYNLETT* **1997**, 411-420. (b) Potin, D.; Williams, K.; Rebek, J.Jr. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1420.
6. Andreu, C.; Galán, A.; Kobiro, K.; de Mendoza, J.; Park, T.K.; Rebek, J.Jr.; Salmerón, A.; Usman, N. *J. Am. Chem. Soc.* **1994**, *116*, 5501-5502.
7. Wang, Z.-H.; Hirose, T.; Baldwin, B.W.; Yang, Y. *J. Chem. Soc. Chem. Commun.* **1997**, 297-298 and references therein.
8. Wintner, E.A.; Rebek, J. Jr. *Acta Chem. Scand.* **1996**, *50*, 469-485.
9. Kato, Y.; Toledo, L.M.; Rebek, J. Jr. *J. Am. Chem. Soc.* **1996**, *118*, 8575-8579.
10. Kocis, P.; Issakova, O.; Sepetov, N.F.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6623-6626.
11. (a) Lonergan, D.G.; Riego, J.; Deslongchamps, G. *Tetrahedron Lett.* **1996**, *37*, 6109-6112. (b) Lonergan, D.G.; Deslongchamps, G., submitted to *Tetrahedron.*
12. An alternative hydroxyimide scaffold was reported recently, see Caycho, J.R.; Garcia-Tellado, F.; de Armas, P.; Marrero-Tellado, J.J. *Tetrahedron Lett.* **1997**, *38*, 7911-7912.
13. Myles, A. CHEM-4000 Honours thesis, U.N.B., **1997**.
14. For a review on nucleotide recognition see Seel, C.; Galán, A.; de Mendoza, J. *Top. Curr. Chem.* **1995**, *175*, 101-132.
15. Domanski, A.; Pielichowski, J. *Zaszyty Naukowe / Wyzsza Szkoly Pedag. im Powstancow Slaskich w Opolu [Ser. A] Chem..* **1981**, *4*, 5-37.
16. Gallant, M.; Link, J.T.; Danishefsky, S.J. *J. Org. Chem.* **1993**, *58*, 343-349.
17. A 5 mM $CDCl_3$ solution of **4** was titrated with a 10 mM $CDCl_3$ solution of 9-EtA until saturation of the imide NH signal. Dilution experiments were carried out by adding aliquots of $CDCl_3$ to host solutions.
18. Titration in 100% DMSO-d6 gave a K_a of 8 M^{-1}.
19. Smithrud, D.B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 339-343.
20. HOSTEST v5.1, Wilcox, C.S.; Glagovich, N.M. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA **1994**.
21. Averaged values based on monitoring 3 different protons on **4**, error represents $\pm \sigma$.
22. MicroCal MCS ITC system: Wiseman, T.; Williston, S.; Brandts, J.F.; Lin, L.-N. *Anal. Biochem.* **1989**, *179*, 131-137.
23. Williams, D.H.; Westwell, M.S. *Chem. Soc. Rev.* **1998**, *27*, 57-63.
24. Schneider, H.-J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1417-1434.
25. (a) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K.-S.; Jones, S.; Parris, K., Williams, K.; Rebek J. Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1082-1090. (b) Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek J. Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090-1094.
26. Hunter, C.A.; Sanders, J.K.M. *J. Am. Chem. Soc.* **1990**, *112*, 5525-5534.
27. Langlet, J.; Claverie, P.; Caron, F.; Boeuve, J.C. *Int. J. Quantum Chem.* **1981**, *19*, 299-338.